DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

MEMORANDUM **Center for Biologics Evaluation and Research - Food & Drug Administration**

From the desk of Dr. Ezio Bonvini
Laboratory of Immunobiology, Division of Monoclonal Antibodies - HFM-564
NIH Campus, Bldg. 29B, Rm. 3NN10, Rockville Pike, Bethesda, MD 20892
Telephone (301) 827-0714 - Facsimile (301) 827-0852 - E-mail bonvini@cber.fda.gov

Date :
(Revision 11: January 28, 2003)

To : BLA File

From : Ezio Bonvini, M.D., Chief, LIB, DMA, OTRR, CBER

Through : Division Director, Division of Monoclonal Antibodies, HFM -555

Subject : BLA STN BL 125036, *alefacept* (Amevive™) for the treatment of moderate to severe plaque psoriasis

LIST OF DOCUMENTS REVIEWED:

1. STN BL 125036/0 Original Submission

All BLA Amendments (1-47), with particular regard to:

2. Amend.007, 08 Mar 2002 (Response to CMC request 11 FEB 2002, 12 FEB 2002, and 15 FEB 2002)
3. Amend.009, 28 Mar 2002 (Response to CMC request 18 Mar 2002: DS and DP validation lot list for consecutive lots)
4. Amend.010, 02 APR 2002 (Revisions to DS)
5. Amend.012, 30 APR 2002 (Response to CMC request 25 Feb 2002: ----------Assay)
6. Amend.013, 10 May 2002 (Changes to DS and DP)
7. Amend.014, 21 May 2002 (Response to CMC inspectional issues)
8. Amend.015, 31 May 2002 (Response to CMC Requests: Cell culture solution hold time & Quality management review))
9. Amend.017, 8 Jul 2002 (Response to CR letter)
10. Amend.022, 13 Aug 2002 (Validation DP at ----------)
11. Amend.024, 28 Aug 2002 (Validation ST at ---------- ----------)
12. Amend.025, 11 Sep 2002 (Stability data commercial DP)
13. Amend.030, 11 Nov 2002 (Follow-up 483 issues)
14. Amend.033, 21 Nov 2002 (label insert)
15. Amend.034, 22 Nov 2002 (label insert)
16. Amend.035, 25 Nov 2002 (label insert)
17. Amend.036, 22 Nov 2002 (label insert and carton)
18. Amend.037, 10 Dec 2002 (label insert and carton)
19. Amend.039, 12 Dec 2002 (diluent WFI CoA and expiry)
20. Amend.041, 13 Dec 2002 (post-approval commitments, see also Am 46)

21. Amend.042, 16 Dec 2002 (label insert)
22. Amend.043, 17 Dec 2002 (label insert)
23. Amend.045, 18 Dec 2002 (label insert and carton)
24. Amend.046, 18 Dec 2002 (post-approval commitments and correction to Am 41)
25. Amend.047, 20 Dec 2002 (label insert)
26. Amend 048, 23 Jan 2003 (label insert)
27. Amend 049, 27 Jan 2003 (post-approval commitments)

PRODUCT DESCRIPTION:
Alefacept is a glycosylated fusion protein. The molecule is composed of the first domain of the human LFA-3 protein fused to the hinge and the constant regions, C_H2 and C_H3, of the human IgG_1 heavy chain. It is expressed in Chinese Hamster Ovary (CHO) cells as a disulfide-linked dimer.

Figure 3-1: Structural Architecture of Alefacept

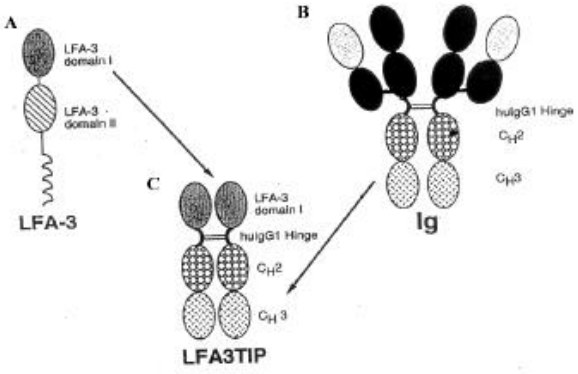

Fig. 3-1: Drawing A depicts the extracellular regions of LFA-3, showing the two domains, I and II. Drawing B shows a schematic of the human immunoglobulin (Ig) molecule, highlighting the hinge and the constant regions (C_H2 and C_H3). Drawing C depicts alefacept, composed of the LFA-3 domain I and the hinge and C_H2 and C_H3 regions of human IgG_1.

Different terms have been used during the pre-clinical and clinical developmental phases as well as in the history of publications pertaining to alefacept. A synopsis is presented below.

Term	**Use**
Alefacept	USAN/INN name for drug substance.
Alefacept for injection	USAN/INN name for drug product.
LFA3TIP	Alternative name for alefacept. LFA3TIP and alefacept are used interchangeably throughout this submission.
AMEVIVE™	Trade name.
BG9273	Biogen product code for alefacept.
BG9273-A or ----- BG9273	BG9273 clinical trial material manufactured at ----------. This material was used in early clinical studies through the initiation of Phase 3 trials.
BG9273-B or ----- BG9273	BG9273 clinical trial material manufactured at Biogen, Inc., Cambridge MA. This material was used in Phase 3 trials.
BG9273-C or ----- BG9273	BG9273 material manufactured by the commercial manufacturing process at Biogen, Inc., Cambridge MA and ----------

----------	Biogen name for alefacept-producing CHO cell line.
BG9712	Biogen product code for clinical material produced by a different CHO cell line (----------). This material was used in several non-pivotal clinical trials and subsequently discontinued.

Alefacept is a ----------

[

]

Chain pairing occurs as combinations of the two splice variants in three possible dimeric configurations: AA, BB, and AB.

PRECLINICAL SECTION

Rationale for use

LFA3 (CD58) binds to CD2 on human T and NK cells humans.

The exact function of CD2 is unknown, but it is involved in APC/T cell interaction and function as a co-stimulatory molecule. CD2 aggregation (by certain pairs of Mab or polyvalent LFA3) can induce T cell activation in vitro and mimics CD3-induced activation. Activation via CD2, therefore has been considered a complementary pathway.

From a molecular mechanism viewpoint, CD2 activation appears to require the expression of CD3. Certain differences, however, merit mention: a. CD2 activation does not appear to phosphorylate the ζ chain of the CD3/TCR complex; and b, it was shown CD2 activation not to involve ZAP70 phosphorylation, a TCR/CD3-induced tyrosine kinase. CD2, therefore, may represent an alternative pathway of activation. A p62 (a GAP-associated adaptor molecule) appears to be selectively phosphorylated in response to CD2 activation and may represent a unique feature of CD2 activation. Interestingly, a similar protein has been implicated in CD28 signaling, a prototypical co-stimulatory molecule. A current view assumes CD2 as a low avidity interaction in the same structural dimension of the TCR/Ag/MHC interaction. This view suggests that CD2 may help in stabilizing the relatively low avidity but specific interaction mediated by the TCR.

A CD2 ligand in the mouse has not been entirely identified: CD48 (a leukocyte antigen of unknown function) is a putative murine ligand; however, human CD48 binds human CD2 poorly. Hence, mouse immunology may not be fully representative of the CD2/LFA3 interaction in humans. CD59, a membrane-bound component of the cytolytic membrane attack complex (MAC) of complement has been proposed as another candidate for binding CD2 in the mouse. Nonetheless, CD2-/- KO mice develop a virtually normal immune system.

LFA3TIP may act by two separate and not mutually exclusive mechanisms: interference with LFA3/CD2 interaction during T cell activation as well as T cell depletion. *In vitro* experiments have demonstrated that both the LFA-3 and Ig portions of alefacept are functional; the LFA-3 domain can bind to its physiological ligand, CD2, and the Ig domain is able to bind Fc receptors (CD16, CD64 and possibly CD32). Both the CD2 and FcR interactions are required for the observed clinical activity of alefacept. LFA3TIP depletes CD2+ cells *in vivo.* LFA3TIP mechanism of action requires the Fc portion of the IgG1 molecule: hence, FCRIII (CD16) binding is necessary. FCRIII is expressed on neutrophils, NK cells and activated macrophages. *In vitro* data suggest that FcRIII-bearing NK cells may be the effector cells that lyse the T cells in an LFA3TIP-redirected, ADCC-like fashion. Of interest, LFA3TIP depleted T cells from the primary organs of CD2-transgenic mice, but left the thymus population intact.

Numerous evidences indicate a role for activated T cells in the pathogenesis of psoriasis. In particular, psoriatic plaques have been shown to contain T cells with a limited TCR repertoire, suggesting a common antigen, that produce type 1 cytokines (e.g., interferon-gamma, IL-2, TNF-alpha), consistent with a TH1 and TC1 effector cell population phenotype.

MANUFACTURING

[

]

Development of Production Cell Line ----------

[

]

Cell banking

The ---------- Master Cell Bank (MCB) used for the production of alefacept was derived from the ---------- ----------. The ---------- MCB and Working Cell Bank (WCB) were prepared for Biogen by ----------). Biogen prepared cells at and beyond the limit of *in vitro* cell age at Biogen, Cambridge, Massachusetts.

[

]

[

]

Testing:
The ---------- MCB, WCB and ---------- were tested for cell line identity, purity, stability and manufacturing suitability.
Identity testing: confirmed the cell line is derived from a Chinese hamster cell line.
Purity testing: confirmed the cell line to be free of adventitious agent contamination. The presence of endogenous retrovirus, as expected for Chinese hamster ovary (CHO) cell lines was confirmed.
Phenotypic and genetic stability: confirmed that the cell line is stable. MCB and WCB are suitable for manufacturing and produce alefacept (BG9273) of appropriate quality.
Cell bank utilization rates: acceptable for the anticipated lifetime of the product. ---- MCB ---------- is used to produce a new WCB of approximately ---- ----------. ---------- WCB ---------- is used to initiate a manufacturing batch at an estimate of ----------
Long-term cell bank storage: programs for the MCB and WCB have been established and described. ------ of the supply is stored in Biogen ---------- and ----- is stored in Biogen ----------. ------- ---------- of each bank are stored offsite at the ----------

[

]

Information on vector generation, full plasmid sequence, cell line characterization and phenotypic stability are all included in the BLA and are adequately presented.
The analysis included (see results below):

Gene Copy Number Analysis ----------

All analyses appeared to confirm the genetic stability of the cell line for manufacturing purposes.

[

]

THESE 2 PAGES

DETERMINED NOT

TO BE

RELEASABLE

[

]

All fermentation and capture components, including media components and amino acids, are ---------- (many are tested as per USP) and are not from animal sources or from processes involving animal-derived materials, except ----------, as listed below.
[

]

In either case, the animal source is acceptable as per current regulations and restrictions: bovine materials used in the processing of intermediates originates from the US, Canada or New Zealand, while the enzymes used in the processing of ---------- is of ---------- origin. CoA's are duly provided.

Action Item: The hold time for the media for the ---------- was not validated in the original submission and in the original manufacturing plan. Biogen filed data (Amend 15) pertaining to the validation of media hold time for the large-scale manufacturing ---------- that employs identical media components, source material, and mixing equipment. The bioburden validation data support a hold time of ----------.

[

]

THESE 10 PAGES DETERMINED NOT TO BE RELEASABLE

Quantitative Composition for Alefacept for Injection

Component	Reference Standard	15 mg Dose Amount in mg[3]	7.5 mg Dose Amount in mg[3]	Function of Component
Alefacept	Biogen	15.0	7.5	Active Substance
Citric acid, monohydrate	USP/EP	0.055	0.055	Buffering agent
Sodium citrate, dihydrate	USP/EP	3.6	3.6	Buffering agent
Sucrose	NF/EP	12.5	12.5	Cryoprotectant
Glycine	USP/EP	5.0	5.0	Caking agent, stabilizer

[

]

Container closures and packaging
AMEVIVE will be supplied in two dosage strengths:
• 15 mg for intramuscular injection
• 7.5 mg for intravenous administration.

The drug is supplied as an “Administration Dose Pack” in two packaging presentations as 1 dose or 4 doses per pack.

15 mg intramuscular dose:
• a vial of sterile water for injection, USP
• a 1 mL plastic, disposable syringe
• 2 needles for IM injection.

7.5 mg intravenous dose:
• a vial of sterile water for injection, USP
• a 1 mL plastic, disposable syringe
• a winged infusion set
• one IM needle used for reconstituting the drug
[

]

Action Item: Upon request for clarification from CBER, Biogen decided to drop the --- mL vial and to supply the package only with the --------10 mL vial (Amendment 17, Item 36).
Now dropped (Amend 17, Question 36)
[

]

Action Item: Upon inquiry, Biogen notified the agency that the expiry on the WFI is 24 months and that their SOP establishes that the expiry dating on the whole package will reflect the DP shelf-life and not the WFI (FAX of 12/11/2002; Amend 39).

It is also noted that the diluent vial (10 mL) greatly exceed the amount necessary for reconstitution. This issue was raised with Biogen in the CR letter of June 6, 2002. Biogen noted in their reply that two factors will limit the quantity of the water that is expected to be withdrawn from the diluent vial: The syringe used for this activity is only a 1 mL syringe, and the syringe is graduated to a high degree of accuracy of 0.01 mL. A third factor needs to be considered. AMEVIVE is intended to be administered by health care professionals who are instructed to withdraw the specified 0.6 mL of diluent for reconstitution and is not intended for self-administration. In consideration of these factors, this reviewer finds the proposed packaging acceptable.

[

]

[

]

Cross reference
Letters of authorization to cross-reference:
• DMF ----------
• NDA ----------
• DMF ----------
were included in the BLA.

Distribution Facilities
The facility for labeling and packaging will be:

Alefacept will be distributed from one of ------ facilities:

• Biogen, ----------

The distribution centers will store packaged drug product at ----------. Quarantine product will be held at PCI or shipped in dedicated refrigerated trucks to ---------- prior to release. Packaged drug product will be released by Biogen Quality Assurance at ---------- upon satisfactory review of all batch production records, production samples, and completion of all release testing. PCI will ship packaged released drug product to Biogen's ------- distribution operation in dedicated ---------- trucks. Shipping validation included.

VALIDATIONS

Process validation and consistency

DS consistency and validation batches

Numerous DS bathes were produced at Cambridge and several more at -----. All parameters appear consistent, with the exception of two outlier batches at the higher limit (within specs) for the ------- potency assay.

[

]

Clearance studies

The purification process was validated to remove all major expected contaminants.

[

]

THIS PAGE WAS

DETERMINED NOT

TO BE RELEASABLE

Clearance of [

]

Assay validations
Assay validation parameters for acceptability of performance (robustness, variability, etc) were provided for [

]

Column lifetime validation
Column lifetime will be determined at the production scale based on ongoing measurement of column performance characteristics as specified earlier.

Adventitious and endogenous agent testing
---------- is tested and demonstrated to be free of adventitious agents.
CNC: A confirmation of no contamination (CNC) is performed on each batch of -------- This assay is designed to detect the presence of bacterial, yeast, or mold microorganisms in test samples.
Mycoplasma: ---------- used to ensure the absence of viable mycoplasma in the ------.
In vitro virus assay: The *in vitro* assay used to detect adventitious viruses is performed using ----------

Virus clearance or inactivation
Since approximately --------- of the unprocessed bulk harvest is required to produce the projected maximum clinical dose of 15 mg, the retroviral load would be ---------- retroviral per dose.

THIS PAGE

DETERMINED NOT

TO BE

RELEASABLE

[

]

Site comparability

Differences between Cambridge and -------- are minimal. Process validation batches and comparability analyses (inclusive of in-process spec comparison) show no differences between the two processes and the DS manufactured at the two sites. In general, a lower degree of variability was observed at the ---- site compared to Cambridge. The major difference between the two sites was in the ----------, which was extensively reviewed in the course of the ----- inspection. The higher level of variability in these parameters at ------ was most likely due to a combination of events, including ----------. The variations were rather small and, more importantly, did not correlate with changes in product quality and purity.

[

]

Reference Standard
A commercial scale batch, ----------, was designated reference standard for material manufactured by the commercial process. ---------- is a representative drug substance batch manufactured by the commercial process at Biogen Inc., Cambridge on ---------- at a batch size of ----------, and was fully characterized in a side-by-side manner with the previous reference standard, ----------, a non commercial size batch ----------. A qualification protocol has been established.

[

THESE 3 PAGES

DETERMINED NOT

TO BE

RELEASABLE

The alefacept reference standard ---------- mg/mL protein in 25 mM sodium citrate, pH 6.8, is ----------. A stability protocol is in place

Stability Protocol for Reference Standard Drug Substance Batch ----------

[

]

COMPARABILITY

Comparability

A comparability assessment plan was included with the BLA submission (S2.6B) and used for comparison of DS lots produced at different sites, with side-by-side studies performed whenever possible.

Biogen conducted analyses in four areas;

[

]

[

]

[

]

Reviewer's assessment: Extensive result and analyses are presented in the BLA. The data support the comparability of the product manufactured at the ----- sites. Furthermore, the comparability protocol is extensive and acceptable for future comparability assessment of changes in drug manufacturing. It is hereby noted that the comparability protocol includes a clinical comparability assessment.

THESE 6 PAGES

DETERMINED NOT

TO BE RELEASABLE

[

]

Stability-indicating parameters
The key stability indicating parameters are therefore ----------

Support for dating period (DP)
The DP appears stable upon storage at ---------- months. For all stability indicating parameters, except ----------, analyses of the two doses demonstrated similar profiles. The 15 mg strength show an ---------- than the 7.5 mg dose strength. No significant trends are observed for the drug product at the ---------- storage temperature of ----------RH for up to --- months. The proposed expiration dating of 24 months at a mean kinetic temperature of 25C (excursions allowed between 15-30C), is acceptable.

In-use stability
Stability under stressed in-use conditions was established

Stability assays
[

]

After reconstitution in the commercial container-closure consisting of ---------- glass vial and ---------- rubber stopper.
Commercial drug product vials from batches -------- and ----------
Reconstituted with sterile water for injection (WFI) per Directions for Use (DFU) instructions in duplicate.
[

]

[

]

---------- syringes (1 mL) and 23 gauge IM ---------- --------- (1.5 inch) are provided below.

Commercial drug product vials from batches ---------- reconstituted with WFI per DFU instructions in duplicate. The contents of the vials were then drawn up in the syringe-needle, and subjected to a number of storage conditions ----------
Samples were ----------
Samples were ----------

[

]

IV dosing set consisting of ---------- tubing, a ---------- ---------- sheath and a --- needle.

[

]

[

]

Action Item: Biological assay for potency were not performed in all cases in the original BLA. Upon request (CR letter), Biogen provided data (Amendment 13) including the assessment of biological potency from stability sample under condition of use. The results show no difference under condition of use in both the ---------- assays for up to --------.

Support for dating period (in-use conditions)
Alefacept is stable and compatible after reconstitution in the commercial container-closure consisting of ---------- glass vial and ----------rubber stopper, when stored under ----------, for up to ----------.
The reconstituted solution is compatible and stable when drawn up in a ---------- syringe---------- needle assembly, and stored ----------
The reconstituted solution is also compatible and stable with IV dosing sets made up of ----- tubing, ------ sheath and a --- needle.
These data support the package insert statement of use within 4 h after reconstitution with storage at 2-8C

SPECIFICATIONS

Specifications were revised from the original BLA upon discussion with CBER. In particular, CBER asked and obtained to maintain certain assays as well as to tighten certain specifications based on their acquired experience. The revised data were provided in Amendment 13 and are listed below.

Alefacept Drug Substance Specifications

[

]

THESE 4 PAGES

DETERMINED NOT

TO BE

RELEASABLE

[

]

An extensive justification for the specifications was included. A brief discussion of critical assays and parameters is presented below

Potency assays
The ---------- validated for use in the determination of the potency of alefacept (BG9273) ----------, and alefacept for injection (drug product).
The potency of alefacept is measured by its ability to ----------
---

Specifications (see above) are identical for the drug substance and drug product.

The ---------- is validated for the use in determination of the potency of alefacept (LFA3TIP) ----------, and drug product.

The potency of alefacept is measured by its ability to ----------
---

Specifications (see above) are identical for the drug substance and drug product.

Detailed SOP, validation data, and specifications are included in the BLA and Amendment 13-15 and 17.

QUESTIONS/COMMENTS FOR SPONSOR

A CR letter was sent on June 6, 2002, including all action items noted in this review and inspectional issues. Biogen provided full and satisfactory answers to all questions in Amendment 13,14, 15, and 17, as noted in the review of the BLA, above.

REFERENCED FDA LICENSES, MASTER FILES, 510K'S, AND AUTHORIZATIONS:

Letters of authorization to cross-reference included in BLA:

Licenses or authorizations cited in BLA:

[

]

CMC ITEMS FOR APPROVAL LETTER

Dating periods

Dating period for DS: 24 months at -70±10C

Dating period for DP: 24 months at a mean kinetic temperature of 25C (excursions allowed between 15-30C

WFI (10 mL vial, Abbott) expiry 24 months (confirmed by CDER)

Stability under condition of use: The data support the package insert statement of use within 4 h after reconstitution with storage at 2-8C

CMC post-approval commitments

Immunogenicity assay

Proposed language: "We acknowledge your commitment (Amendment 17, Answer to question 48, dated July 8, 2002) to develop by [date] a quantitative assay capable of discriminating an immunogenic response directed against the LFA3 portion from one directed against the IgG1 Fc portion of your molecule. "

Biogen indicated in their Amendment 17 their intention to develop a ---------- to characterize the antibody response in sera of alefacept-treated subjects. The proposed assay will be able to qualitatively discriminate anti- LFA3 antibodies from anti-IgG1 Fc antibodies. This assay will rely on the identification the presence of anti-alefacept antibodies using the validated screening and titration ---------- combined with the ----------assay. A description of the proposed assay was included in Amendment 17.

Continued stability program:

At least one lot each year from each manufacturing site (if manufacturing at that site is taking place). (Amendment 13)

FINAL RECOMMENDATION

Based on the CMC data submitted the BLA is recommended for approval.